REMARKS

Claims 1-7 and 9-17 have been rejected under 35 U.S.C. §112, second paragraph, as indefinite. Specifically, the examiner asserted that in claim 1 the recitation "wherein said one or more specific antibodies are each specific for a particular MHC allele" is vague and indefinite. A similar comment was made with regard to claim 2. Applicants respectfully submit that this rejection has been obviated by the amendments set forth above to claims 1 and 2. Claim 20 also has been similarly amended to retain consistency with claim 1.

The examiner has maintained his previous rejection of claims 1-7, 14, 15 and 25 under 35 U.S.C. §102 as anticipated by the teachings of Walter et al., *International Immunology* 9(3):451-459 (1997). He also has maintained his previous rejection of claims 1-3 under 35 U.S.C. §102 as anticipated by U.S. Patent 6,528,304, issued to Carosella et al. Both references disclose the binding of a specific antibody, W6/32, to a specific recombinant HLA molecule and the subsequent detection of the bound antibody. The examiner has asserted that the antibody is specific to a specific recombinant HLA molecule since the antibody is specific to class I molecules in general as opposed to Class II molecules. These rejections are traversed.

As set forth above, applicant has amended the pending claims to make clear that the claims are directed to recombinant molecules which detect individual allele specific antibodies. In contrast, the antibodies of the cited prior art simply recognize the class of MHC (or HLA) molecules. The amendments are based on the specification, which make reference to the detection of different alleles. See for example, page 8, line 24, and page 17, from line 1, which refers to the use of different individual recombinant MHC molecules "e.g. relating to one or more epitopes of a naturally occurring allele." As the cited references only disclose antibodies which recognize a single class of molecule, and cannot further differentiate and recognize a single, particular molecule within the class, the references do not anticipate the cited claims.

The examiner also has newly rejected claims 1 and 2 under 35 U.S.C. §102(b) as anticipated by Viken et al., *Human Immunology* 44:63-69 (1995). The examiner asserted that the reference discloses detecting antibody reactivity with samples of antibodies to HLA-DQ2 molecules which have been transfected and further disclosed the use of secondary antibodies. This rejection is traversed.

Claims 1 and 2 have been amended to refer to detection of the antibodies in a sample of body fluid. Claim 16 has been

amended to specify that the body fluid sample is blood or derived from blood, as taught on page 16 of the specification. Viken et al. perform their method in cell culture and there is no indication in the reference that the methods could be used for detection of antibodies in samples of body fluid.

The examiner has maintained his previous rejection of claims 1-7, 9-17, 20 and 22-25 under 35 U.S.C. §103, as obvious over U.S. Patent 5,270,169, issued to Chang et al. in view of the Walter et al. reference cited above. The examiner asserted that Chang et al. disclose a method of detecting the presence of anti-HLA antibodies by using HLA antigens which may be synthetic and that the only difference between this reference and the present claims was that Chang et al. did not suggest the use of recombinant antigens. Such antigens, however, he said, were taught by the secondary reference. This rejection again is traversed.

As amended above, the pending claims of this application now explicitly set forth a method for detecting the presence of at least one allele-specific MHC or HLA antibody within a group of MHC or HLA molecules. Each allele specific antibody is specific for a particular naturally occurring MHC allele and binds to only one of the recombinant MHC or HLA molecules which contains at least one epitope of the naturally occurring allele. In contrast

to this method for detecting whether a very specific antibody is present in a sample, the cited references disclose only antibodies which recognize a class of MHC or HLA molecules. The combined teachings of these two references do not teach the identification of allele specific antibodies, as the present claims as amended above now more explicitly require. There is no suggestion in either reference, whether considered independently or in combination, of the identification of allele specific antibodies.

This distinction is evidenced in the Example provided by Chang et al., in which the method taught is unable to detect different HLA alleles. Instead, the experiment simply determines if any antibodies are present in the sample by binding to HLA antigens obtained from a cultured supernatant of a lymphoblastoid cell line. Thus, clearly one method advocated by Chang et al. is the determination of HLA antibodies in general in a sample, i.e. not allele specific. In performing such methods, retention of the crucial epitopic integrity that distinguishes different HLA alleles is not of paramount importance. In such a case, loss of absolute epitopic integrity can be tolerated. It was believed at the time of the invention that framework components of HLA molecules to which monomorphic antibodies such as W6/32 bind were not as sensitive to disruption as allele-specific epitopes. As

such, the skilled person would possibly consider the use of synthetic MHC molecules if detection of classes of antibodies, rather than allele-specific antibodies, was contemplated. The reference in Chang et al. to synthetic HLA molecules thus should be read in this context.

In contrast, it was the view at the time of the invention, as noted above, that the epitopic integrity which uniquely identifies an MHC allele would be lost when produced recombinantly. As such, the use of recombinant molecules in methods such as those described in the present application would not be thought possible using recombinant molecules and, indeed, are not advocated by Chang et al.

The secondary reference does not compensate for the deficiencies of the primary reference. The Walter et al. reference teaches that W6/32 binds recombinant HLA antigens. However, this antibody is well known to be directed to a monomorphic region of the antigen present in class I antigens. Retention of this epitope in recombinant molecules would not lead the skilled person to believe that polymorphic epitopes would be retained in recombinant molecules. The W6/32 antibody binds to framework portions of the HLA molecule, whereas allele-specific antibodies bind to epitopes previously thought to be sensitive to recombinant expression. Although Applicants dispute that the

skilled person would seek to combine these documents in the first place, even if one were to do so at best he would find a teaching of the use of general antibodies which can identify a class of HLA molecules in the method of Chang et al. to identify synthetic HLA molecules of a particular class. The secondary reference does not teach that allele-specific antibodies can be detected using recombinant HLA molecules.

The Applicants' work in establishing that recombinant molecules actually could be used to identify allele-specific antibodies and that the effects of glycosylation and the use of non-specific peptides did not lead to a loss of relevant allele-specific epitopic sites has allowed, for the first time, the development of a method of detecting specific MHC antibodies which was not previously possible. They have provided a method which is able to detect specific antibodies to specific MHC alleles which simply was not possible with earlier techniques which used isolated MHC molecules which contained pools of antigens which would consist of more than a single allele.

Claim 20 has been rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent 6,528,304, issued to Carosella et al. in view of U.S. Patent 5,420,016, issued to Boguslaski et al. The examiner asserted that Carosella et al. differed from the subject matter of claim 20 in failing to teach packaging

components into a kit but that Boguslaski et al. teach that assembling components into test kits adds to the convenience and ease of use by the test operator. This rejection is traversed.

The shortcomings of the Carosella et al. patent have been discussed above and that discussion is equally applicable to the present rejection. Carosella et al. disclose immunoprecipitation of K562-8 HLA-G2 cells carrying recombinant HLA with a specific antibody, W6/32, which is not allele specific. The kit described in claim 20 comprises a recombinant MHC molecule which binds a specific MHC antibody allele and means for detecting antibodies, rather than the antibody itself. If the recombinant MHC molecule of the Carosella et al. reference, however, were to be provided in a kit, as Carosella et al. do not provide free MHC molecules, the cell itself from Carosella would have to be provided in the kit to fall within the scope of the claim. As it is only the tools for a method that are provided in the kit and not the samples to be tested, the recombinant molecules of Carosella et al. would not be provided in kit form.

The cited secondary reference does not compensate for the deficiencies of the primary reference. Boguslaski et al. do not teach or suggest a kit comprising one or more recombinant MHC molecules having the key characteristics as set forth in claim 20, namely, that each of the recombinant molecules binds to a

different allele specific MHC antibody. Accordingly, the cited references do not render obvious the kit claimed in claim 20.

Finally, the examiner has maintained his previous rejection of claims 24-28 under 35 U.S.C. §103 as obvious over the teachings of Chang et al. in view of Walter et al. and further in view of a reference by Luxembourg et al. For the reasons set forth above in relation to the patentability of the claims from which these claims depend, Applicants again submit that the primary and secondary cited references do not render obvious the detection of allele-specific antibodies using recombinant MHC molecules. The addition of the teachings of Luxembourg et al. does not overcome the deficiencies of the other references.

The recombinant MHC molecules that were generated were suggested for use in T-cell antigen receptor recognition via the peptide rather than by recognition of unique epitopes of the MHC molecule. Therefore, the best that Luxembourg et al. would seem to show is that recombinant MHC antigens are suitable for peptide presentation. They do not, however, show that epitopic sites which discriminate different MHC alleles could be retained. As Applicants have argued in previous submissions, T cells utilize a different epitope on the MHC or HLA molecules in comparison to antibodies, and thus T-cell binding to recombinant molecules is

not illustrative of any utility of recombinant molecules for antibody binding.

Luxembourg et al. teach nothing about the use of recombinant molecules for the isolation of allele-specific anti-MHC antibodies. The examiner indicates that the reference teaches that use of the system for the isolation of peptides such as antibodies. The passage to which the examiner refers, however, is merely concerned with quantifying the number of MHC molecules immobilized per bead. The ability of recombinant molecules to bind to naturally occurring antibodies-and more particularly whether they would be able to be discriminated by allele-specific antibodies is simply not addressed. As such, none of the documents, considered alone or in combination, provides the relevant teaching to make obvious claims 24-28 of the present application.

Applicants respectfully submit that in view of the amendments and discussion set forth above, the pending claims of the application now are in condition for allowance.

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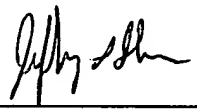
Signature				*Date*	14 December 2005
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